



NTP
National Toxicology Program

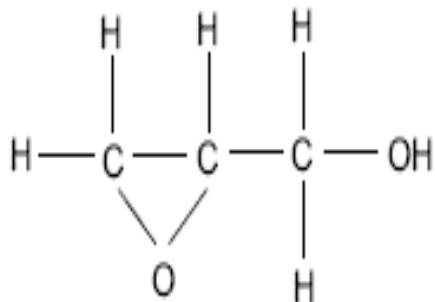
Toxicology and Carcinogenesis Studies in Haploinsufficient $p16^{\text{Ink4a}}$ / $p19^{\text{Arf}}$ N2 Mice (B6.129-Cdkn2a^{tm1Rdp})

Glycidol - GMM 13





Haploinsufficient p16^{Ink4a} /p19^{Arf} Mice Glycidol Studies



Glycidol

CAS No. 556-52-5

$C_3H_6O_2$

MW 74.08

- Chemical intermediate
- Stabilizer in the manufacture of vinyl polymers
- Additive for oil and synthetic hydraulic fluids
- IARC - Group 2A - probable human carcinogen
- NTP ROC - reasonably anticipated to be a human carcinogen



NTP Studies: Glycidol Multisite Carcinogen

Glycidol TR 374 (oral gavage) - F344 Rat and B6C3F1 Mouse

Male Rat

Mesothelioma

Mammary gland

Brain

Forestomach

Intestine

Skin

Zymbal gland

Thyroid

Female Rat

Mammary gland

Brain

Oral mucosa

Clitoral gland

Thyroid

Leukemia

Lung

Male Mouse

Harderian gland

Forestomach

Skin

Liver

Skin

Female Mouse

Harderian gland

Mammary gland

Uterus

Subcutaneous tissue

Negative in male and female p53(+/-) mice

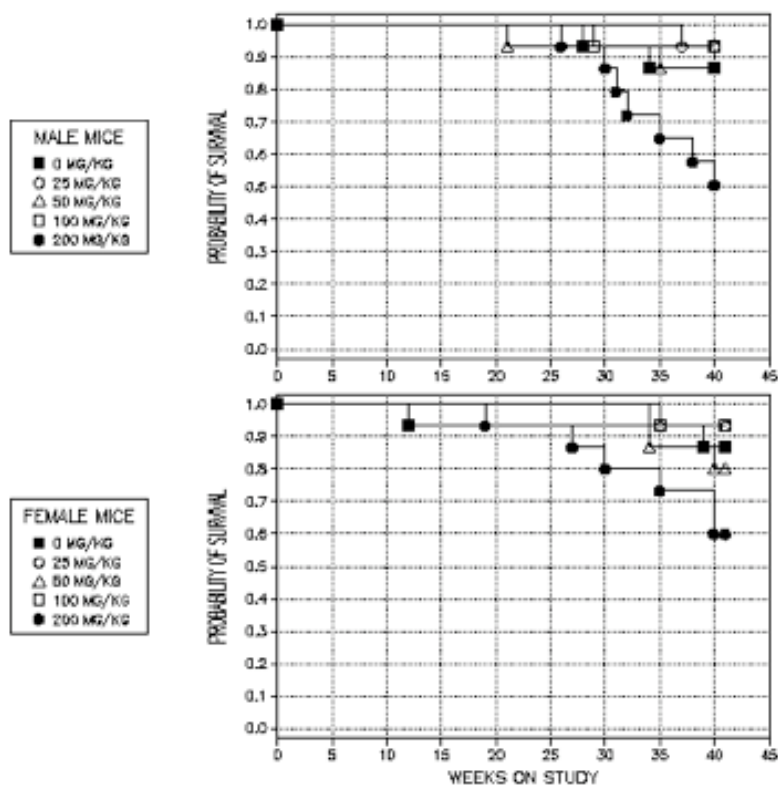


Glycidol Oral Gavage Study Designs:

- Doses selected to overlap NIEHS/NTP Glycidol study doses
 - NTP 2-year B6C3F1 mouse study
 - 0, 25, 50 mg/kg
 - NIEHS 26-week p53(-/+) mouse study
 - 0, 25, 50 mg/kg
- NTP 40-week haploinsufficient p16^{INK4a}/p19^{Arf} mouse study
 - 0, 25, 50, 100, 200 mg/kg
 - 15 animals/dose/sex

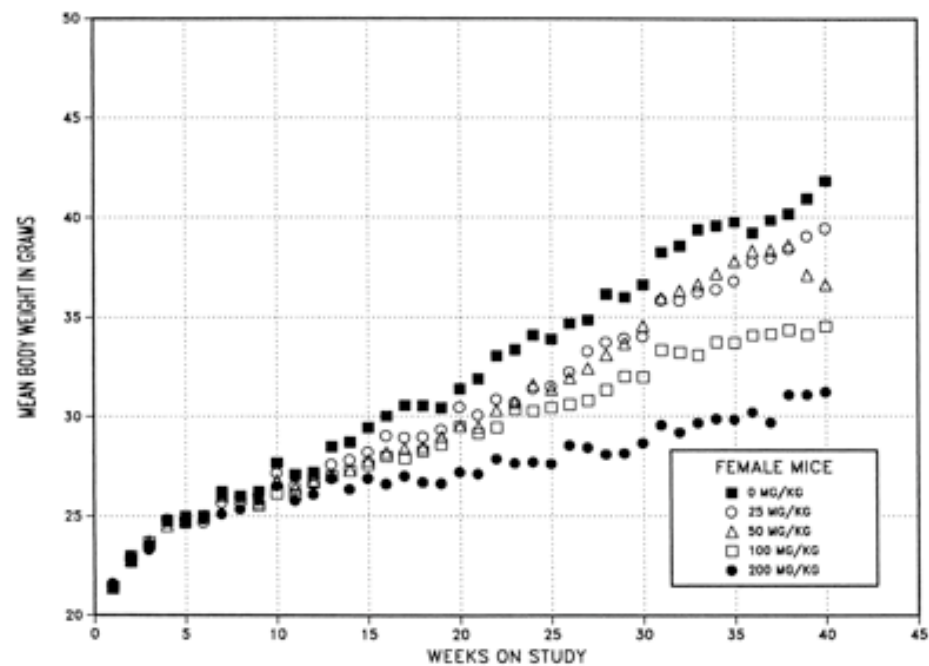
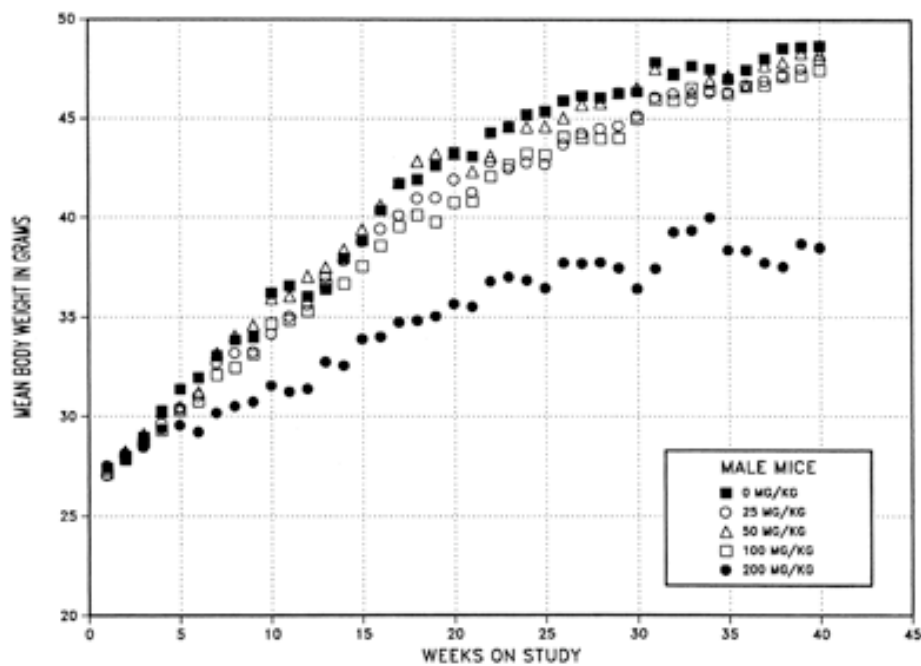


Survival Curves for 40-week Glycidol Study in Haploinsufficient p16^{Ink4a}/p19^{Arf} Mice





Body Weight - Male and Female Mice





Glycidol: Males & Females - Neoplastic Lesions - Histiocytic Sarcomas

Dose (mg/kg)	0	25	50	100	200
Males	2/15** ^a (13%)	6/15 (40%)	9/15** (60%)	5/15 (33%)	11/15** (73%)
Females	9/15 (60%)	9/15 (60%)	12/15 (80%)	10/15 (67%)	13/15 (87%)

**p ≤ 0.01

^aTrend statistic



Glycidol: Males - Neoplastic Lesions - Lung

Dose (mg/kg)	0	25	50	100	200
Alveolar/Bronchiolar Adenoma	1/15 (7%)	0/15 (0%)	2/15 (13%)	7/15* (47%)	3/15 (20%)
Alveolar/Bronchiolar Carcinoma	2/15 (13%)	1/15 (7%)	1/15 (7%)	3/15 (20%)	0/15 (0%)
Alveolar/Bronchiolar Adenoma or Carcinoma	3/15 (20%)	1/15 (7%)	3/15 (20%)	8/15 (53%)	3/15 (20%)

*p ≤ 0.05



Glycidol: Females - Neoplastic Lesions - Lung

Dose (mg/kg)	0	25	50	100	200
Alveolar/Bronchiolar Adenoma	0/15 ^{**a} (0%)	1/15 (7%)	0/15 (0%)	1/15 (7%)	4/15 [*] (27%)
Alveolar/Bronchiolar Carcinoma	0/15 (0%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	0/15 (0%)
Alveolar/Bronchiolar Adenoma or Carcinoma	0/15 ^{**a} (0%)	1/15 (7%)	0/15 (0%)	2/15 (13%)	4/15 [*] (27%)

* $p \leq 0.05$ ** $p \leq 0.01$

^aTrend statistic



Glycidol: Males and Females - Nonneoplastic and Neoplastic Lesions of the Forestomach

Dose (mg/kg)	0	25	50	100	200
Males: epithelium hyperplasia	0/15** ^a (0%)	1/15 (7%)	1/15 (7%)	0/15 (0%)	6/15** (40%)
Males: squamous papilloma	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	1/15 (7%)
Females: epithelium Hyperplasia	0/15 (0%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	4/15* (27%)
Females: squamous papilloma	0/15** ^a (0%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	3/15 (20%)

* $p \leq 0.05$ ** $p \leq 0.01$

^aTrend statistic



Glycidol: Males - Non-neoplastic Brain Lesions

Dose (mg/kg)	0	25	50	100	200
Neuronopathy	0/15	0/15	0/15	0/15	5/15*
Gliosis	0/15	0/15	0/15	0/15	4/15*
Hemorrhage	0/15	0/15	0/15	0/15	2/15

* $p \leq 0.05$



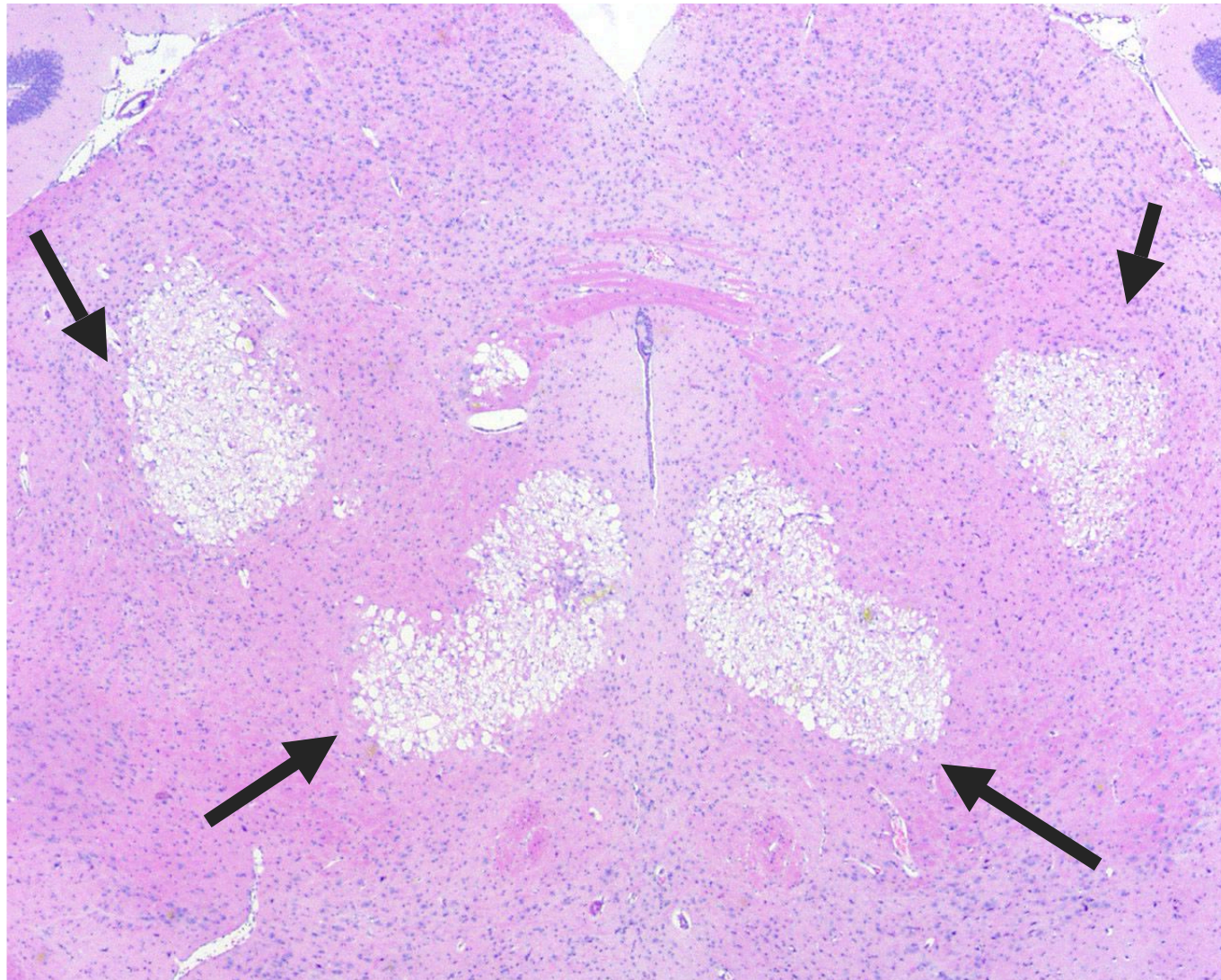
Glycidol: Females - Non-neoplastic Brain Lesions

Dose (mg/kg)	0	25	50	100	200
Neuronopathy	0/15	0/15	0/15	1/15	4/15*
Gliosis	0/15	0/15	0/15	0/15	4/15*
Hemorrhage	0/15	0/15	0/15	1/15	0/15

* $p \leq 0.05$



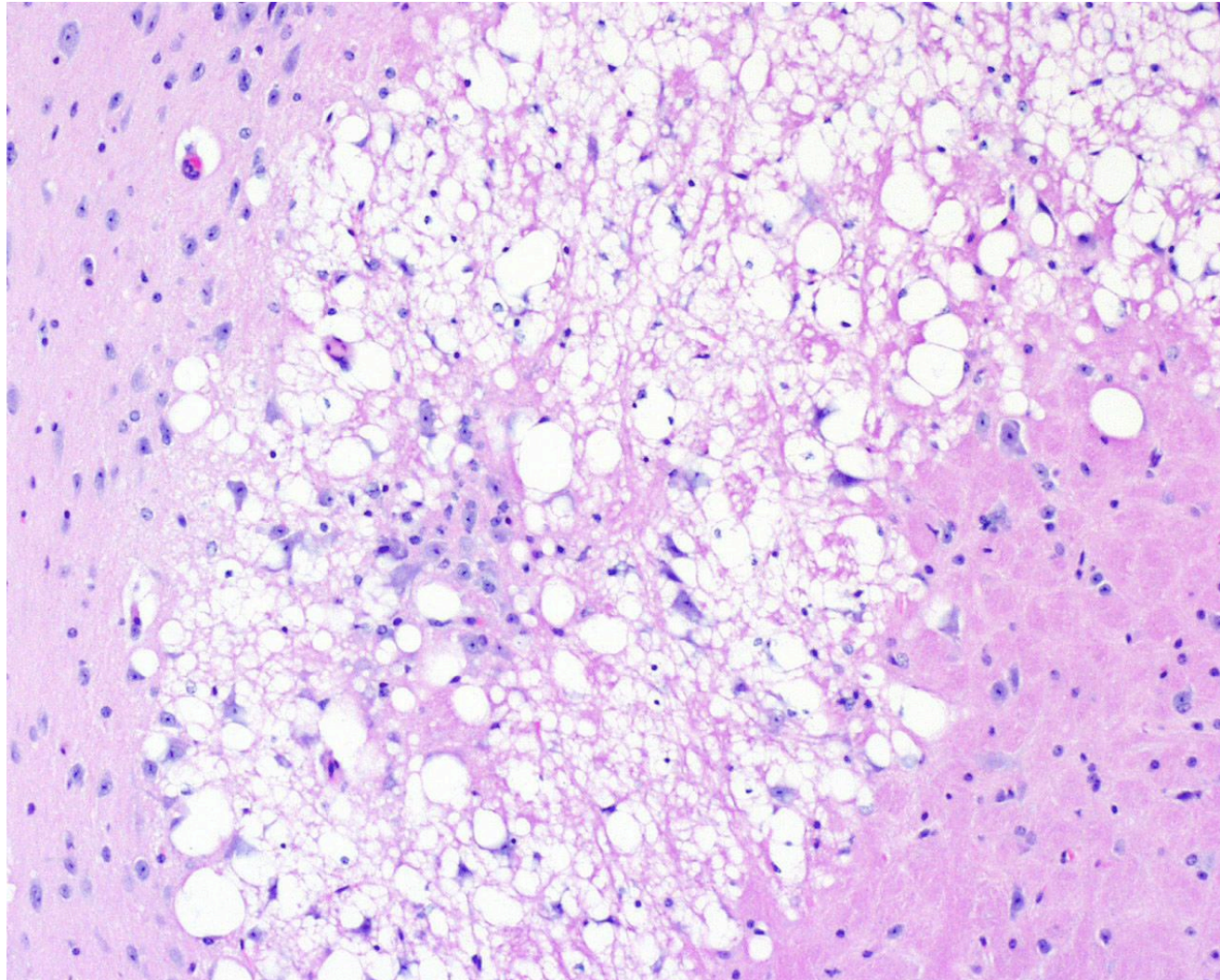
Neuronopathy - symmetrical vacuolization, midbrain nuclei



Thalamus



Neuronopathy - vacuolization of neurons and glial cells



Thalamus



Glycidol Conclusions

- ***Clear evidence of carcinogenic activity*** in male haploinsufficient p16^{Ink4a} /p19^{Arf} mice
 - Histiocytic sarcomas
 - Alveolar/bronchiolar adenomas
- ***Some evidence of carcinogenic activity*** in female haploinsufficient p16^{Ink4a} /p19^{Arf} mice
 - Alveolar/bronchiolar adenoma
 - Forestomach papillomas
- Treatment-related forestomach and brain lesions in male and female mice
 - Forestomach hyperplasia
 - Neuronopathy